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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/869,159	08/15/2001	Tania Kastelic	1556.0290000	9266

7590 12/28/2004

Sterne Kessler
Goldstein & Fox
Suite 600
1100 New York Avenue NW
Washington, DC 20005-3934

EXAMINER

QIAN, CELINE X

ART UNIT PAPER NUMBER

1636

DATE MAILED: 12/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/869,159

Applicant(s)

KASTELIC ET AL.

Examiner

Celine X Qian Ph.D.

Art Unit

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 October 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3-9 and 15-48 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,3-9 and 15-48 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 25 June 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claims 1, 3-9, 15-48 are pending in the application.

This Office Action is in response to the Amendment filed on 10/4/04.

Response to Amendment

The rejection of claims 4, 6, 16 and 17 under 35 U.S.C.102 (b) is maintained for reasons set forth of the record mailed on 6/3/04 and further discussed below.

The rejection of claims 1, 3, 5, 7-9 and 15 under 35 U.S.C.103 (a) is maintained for reasons set forth of the record mailed on 6/3/04 and further discussed below.

Newly added claims 18-48 are rejected under 35 U.S.C. 103 (a) for reasons discussed below.

Newly claims 47 and 48 are rejected under 35 U.S.C.112 2nd paragraph for reasons discussed below.

Response to Arguments

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 4, 6, 16 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Zubiaga et al.

In response to this rejection, Applicants argue that Zubiaga does not disclose an expression cassette consisting of one or more reporter genes encoding a protein which gives a

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detectable signal. Applicants argue that the plasmid construct disclosed by Zubiaga encodes a β -globin protein, which is not a reporter gene that encodes a protein which gives a detectable signal. Applicants further argues that the plasmid construct disclosed in Zubiaga does not consist of an instability region inserted into the 3' UTR sequence of a reporter gene as recited in the present claims. Applicants assert that this plasmid consists of a 53 base pair spacer region between the β -globin coding region and an ARE sequence inserted prior to the 3' UTR of the gene, thus the ARE sequence is not inserted into but just fused between the 3' UTR sequence of the reporter gene as required by the instant claims. Applicants thus conclude that the disclosure of Zubiaga does not anticipate the instant claims.

These arguments have been fully considered but deemed unpersuasive. The teaching of Zubiaga is discussed in detail in the previous office action. In response to the argument of the reporter gene, Applicants are reminded that the specification does not give a definition for this term. As such, the term encompasses any gene that is able to give a detectable signal and serve for reporter purpose. Absent evidence from the contrary, this limitation does not exclude the gene encoding β -globin protein, in which the signal can be measured at mRNA level (as taught in Zubiaga et al.) or by an antibody to said protein. Therefore, Zubiaga has taught this limitation in its disclosure.

In response to the argument of inserting the ARE sequence into 3' UTR, Applicants are reminded the structure of the plasmid taught by Zubiaga is same as the expression cassette recited in the claims. Whether the ARE sequence is inserted or fused into the 3'UTR of the β -globin gene does not impart a structural difference between these two construct. In fact, Zubiaga discloses that the ARE sequence from c-fos is inserted in the 3' UTR of β -globin gene (see page

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2220, 2nd col., 6th paragraph, lines 1-6, and lines 6-10). Therefore, Zubiaga discloses every elements of the claimed invention. This rejection is maintained.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 3 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Banhozler et al., Zubiaga et al., in view of Zhang et al.

In response to this rejection, Applicants argue that there is not motivation for one of ordinary skill in the art to combine the teaching of Banhozler et al. and Zhang et al. thus to replace the IL-3 with GFP. Applicants argue that Banholzer provides not indication that such a modification is desirable or necessary because quantification of mRNA is required by this method. Furthermore, Applicants argue that Zubiaga does not disclose the use of a reporter gene that expresses a protein that gives a detectable signal, thus it does not cure the deficiency of either Banhozler and Zhang. Moreover, Applicants argue that there is no motivation to insert the instability sequence disclosed in Zubiaga into the plasmids used in the methods for Banholzer, and Zubiaga does not teach the insertion of instability region to the 3' UTR of a reporter gene. Applicants assert that Zubiaga and Banzhozler do not disclose all the limitation of the claims. Lastly, Applicants argue that Zhang does not disclose, suggest or contemplate the insertion of a heterologous region into the 3' UTR sequence of a reporter gene. Applicants thus conclude that the claimed invention is not obvious.

These arguments have been fully considered but deemed unpersuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by

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attacking references individually where the rejections are based on combinations of references.

See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091,

231 USPQ 375 (Fed. Cir. 1986). The examiner recognizes that obviousness can only be

established by combining or modifying the teachings of the prior art to produce the claimed

invention where there is some teaching, suggestion, or motivation to do so found either in the

references themselves or in the knowledge generally available to one of ordinary skill in the art.

See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347,

21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the motivation to combine the references is

ample because Banholz et al. has demonstrated that compounds such as rapamycin can be

tested for its ability to affect mRNA instability in a construct comprising the mRNA sequence

down stream of the AP gene. Since the ARE instability region has already been identified as

taught in Zubiaga et al., it can be inserted to 3'UTR of any known gene, including a reporter

gene such as GFP. One of ordinary skill in the art would have been motivated to do so because

the advantages offered by a GFP reporter over measuring mRNA stability by Northern blot, such

as the non-invasive nature of direct measurement of fluorescent intensity. The method taught by

Banholzer is just one example of using a specific instability sequence to screening for

compounds which affect mRNA stability. An ordinary artisan would recognize other sequences

include the ARE taught by Zubiaga can also be used in such a system to screen compounds that

affect such instability sequences. In addition, the signal produced by GFP is also quantifiable.

As such, the combined teaching of Banholzer, Zubiaga and Zhang teach every limitation of the

claimed invention, and also provide motivation to combine the teachings. Therefore, the

invention is obvious in view of these teachings. This rejection is maintained.

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Newly added claims 18-20, 23-25 and 46 are rejected for same reasons as applied to claims 1, 3 and 15 set forth in the previous office action and discussion above.

Claims 5, 7-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zubiaga et al., in view of Maniatis et al.

In response to this rejection, Applicants argue that Zubiaga does not disclose an expression cassette comprising a reporter gene which encodes a protein which gives a detectable signal and the plasmid does not consist of an instability region inserted into 3' UTR sequence of the reporter gene. Applicants further argue that these deficiencies are not cured by Manniatis, which only teaches a method of stable transfection. Applicants thus conclude that the invention is not obvious.

These arguments have been fully considered but deemed unpersuasive. For reasons given above (in the 102 rejection section), Zubiaga does teach an expression cassette comprising a reporter gene which encodes a protein which gives a detectable signal, and said construct consist of an instability region in the 3' UTR sequence of the reporter gene. Therefore, the claimed invention is obvious in view of the combined teaching of Zubiaga and Manniatis for reasons discussed in the previous office action. This rejection is maintained.

New Grounds of Rejection Necessitated by Applicant's Amendment

Claim Rejections - 35 USC § 103

Claims 21, 22, 26 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Banhozler et al., Zubiaga et al., in view of Zhang et al.

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The teachings of Banhozler, Zubiaga were discussed in the previous office action.

However, Banhozler et al. does not teach using an enzymatic reporter gene in the expression construct.

The teaching of Zhang et al. was discussed in the previous office action. Zhang also teaches reporter genes such as SEAP, firefly luciferase, CAT can be using to quantifying transfection efficiencies and assayed in conditioned mediums (see page 707, 2nd paragraph).

As discussed previously, it would have been obvious to one of ordinary skill in the art to develop a method of screening compound that induce mRNA instability by using an expression cassette comprising a GFP reporter gene and a mRNA instability sequence inserted into 3'UTR of said reporter gene based on the teaching of Banhozler et al., Zubiaga et al., and Zhang et al. It would also have been obvious to use an enzymatic reporter gene such as SEAP or β -gal as taught by Zhang. One of ordinary skill in the art would have been motivated to do so for the ease of measuring the enzymatic signal over measuring mRNA stability by Northern blot. The level of skill in the art of molecular cloning is high. Absent evidence from the contrary, one of ordinary skill in the art would have reasonable expectation of success to make an expression cassette comprising an enzymatic reporter and mRNA instability sequence to screen for compounds that induce mRNA instability. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill of art at the time the invention was made.

Claims 28-32, 34-38, 47 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zubiaga et al., in view of Zhang et al.

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The teaching of Zubiaga et al. was discussed in the previous office action. However, Zubiaga et al. does not teach a reporter gene DNA expression system comprising an expression cassette consisting of one or more genes encoding a protein having a detectable signal, wherein the protein is a fluorescent protein or an enzyme.

The teaching of Zhang was discussed in the previous office action and above.

It would have been obvious to one of ordinary skill in the art to make a reporter gene construct comprising an expression cassette comprising a GFP or an enzymatic reporter gene such as SEAP and a mRNA instability sequence inserted into 3'UTR of said reporter gene based on the teaching of Zubiaga et al., and Zhang et al. One of ordinary skill in the art would have been motivated to do so because the advantages offered by a GFP reporter over measuring mRNA stability by Northern blot, such as the non-invasive nature of direct measurement of fluorescent intensity. One of ordinary skill in the art would also have been motivated use enzymatic reporter for the ease of the procedure rather than measuring mRNA stability by Northern blot. The level of skill in the art of molecular cloning is high. Absent evidence from the contrary, one of ordinary skill in the art would have reasonable expectation of success to make an expression cassette comprising a GFP reporter or an enzymatic reporter and mRNA instability sequence to screen for compounds that induce mRNA instability. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill of art at the time the invention was made.

Claims 33, 39-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zubiaga et al., Manniatis et al. and Zhang et al.

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The teachings of Zubiaga et al. Miannatis et al. and Zhang et al. were discussed in the previous office action. However, Zubiaga et al. does not teach a cell transfected cell line comprising a reporter gene DNA expression cassette comprising a GFP or an enzymatic reporter.

As discussed in the previous office action, it would have been obvious to one of ordinary skill in the art to stably transfect the cell line with two expression systems as taught by Zubiaga et al. The ordinary artisan would have been motivated to do so for the ease of use of said cell line so that one does not have to transfect the cell line every time a compound needs to be tested. Using stably transfected cell line or transient transfected cell line for an assay is interchangeable and routine experimentation in the relevant art. The ordinary artisan would have reasonable expectation of success because of the teaching of Zubiaga et al., who teach an assay system comprising a cell line transfected reporter construct and control construct can be used to measure mRNA stability, and the teaching of Maniatis et al., who teach a method to stably transfect mammalian cells. As discussed above, one of ordinary skill in the art would also have been motivated to use GFP as reporter in the construct taught by Zubiaga because the advantages offered by a GFP reporter or other enzymatic reporter over measuring mRNA stability by Northern blot, as taught by Zhang et al. The level of skill in the art of molecular cloning is high. Absent evidence from the contrary, one of ordinary skill in the art would have reasonable expectation of success to make the claimed invention. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill of art at the time the invention was made.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

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The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 47 and 48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The word "derived" renders the claims indefinite because the nature and number of derivative process are unknown. As such, the metes and bounds of the claims cannot be established.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian Ph.D. whose telephone number is 571-272-0777.

The examiner can normally be reached on 9:30-6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Celine X Qian Ph.D.
Examiner
Art Unit 1636



**DAVE TRONG NGUYEN
PRIMARY EXAMINER**